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CYTOKINES IN URINE INDICATES URETHRAL ORIGIN OF URGENCY IN THE "OVERACTIVE BLADDER SYNDROME".

Hypothesis / aims of study

The non-existence of bladder pathology or anatomical signs of muscular overactivity in the so called Overactive Bladder Syndrome (OAB-syndrome) has puzzled urologists and uro-gynecologists for years.
Theories on the possibilities of the symptoms originating from the urethra have been discussed but not confirmed. The clinical observation of a coexistence of urethral tenderness and OAB raised a new interest for the hypothesis that the urethra plays a major role in the OAB-syndrome.

Study design, materials and methods

The study is summary of results obtained for clinic reasons after informed consent including written information and according to the rules of the Helsinki declaration.
The study was initiated after a clinical observation in ten consecutive patients complaining of OAB, as a majority reported urethral tenderness, and/or had an easily palpable urethra at a routine vaginal examination.
The results presented are from a total material of eighty consecutive patients applying for urgency and/or urgency incontinence. All patients were "toilette mapping", had negative urine cultures and were using pads to for "safety" reasons.
Urine diaries were collected for 2 x 24 h before and after treatment. 65 patients reported > 7 sessions a day. After inclusion, a cystoscopy with estimation of bladder volume was performed. In 50 patients a tissue sample was obtained from the urethra for clinical reasons. The sample was used also for immunohistology.
Treatment was given in a standardized procedure with an intraurethral application of a group-I-corticosteroid ointment (Terracortril with Polymyxin B^{R}) and urethral massage at four sessions within two weeks.
In 10 patients with "OAB-.syndrome" after additional informed consent a "dry" massage with a semi filled bladder was performed before treatment. The patients were then asked to urinate in two portions. The same procedure was performed in 10 healthy controls. The urine was analyzed for cytokines.

Results

Two patients were excluded due to concomitant medication in spite of information.
Twenty-one patients (33%) reported a "dry" urge from start. Bladder capacity was normal in almost all patients; less than 6% (4/63) complained of urgency during bladder filling for cystoscopy.
Application of a mild steroid in the urethra combined with massage decreased voiding frequency and urgency in all but one patient. The decrease, though being numerically low, was statistically highly significant.
14 patients who reported "wet" urge from start, stopped leaking (29%), while another 21 reported fewer problems (43%)
The only patient who reported more leak after treatment than before, at the same time reported fewer sessions after treatment (15 + 12/ 24h) than before (17+16/24h).
In 43/50 patients routine microscopy of tissue from the urethra showed mild or moderate inflammatory reaction at specific questioning. In 22 patients T-cells were the dominating cell-type, in 9 patients B-cells were dominating. In 5 patients the pathologist reported of the coexistence of both T- and/or B- lymphocytes.
In no sample was the inflammation a very obvious finding though three samples showed squamouse cell metaplasia – usually linked to inflammation.
One of the 3 patients without any sign of inflammation had a bladder volume of only 75 ml.
In 6/10 patients with urgency or urgency incontinence, interleukin 8 (IL-8) after massage of the urethra was elevated before treatment (> 200 ng/L) while it was elevated in only 3 out of 10 controls.
The level was higher in the first urine portion than in the second, and the difference in interleukin concentration between the two portions obtained was higher in the first urine portion in patients with urgency than in the control group (mean difference: 600 ng/l in patients and 180 ng/l in the controls).
Interleukin 2, 4 and 6 as well as Interferon gamma did not react in any of the patients.
Only four out of sixtyfive patients accepted an offer of additional pharmacological treatment after the massage treatment.
Another 3 patients had recidivating problems within the follow up time which is ongoing since more then one year.

Interpretation of results

The results, with less urgency and less incontinence after local, anti-inflammatory treatment of the urethral mucosa make it reasonable to conclude that the urgency sensation may originate from the urethra. The difference in IL- 8 in the urine of patients with urgency before and after a "dry" urethral massage and the lower concentration in the urine of healthy controls after the same procedure, as well as the pathologic/anatomic findings with dominating T-cells indicate that some sort of urethral inflammation, though low graded, may be involved in urgency and urgency incontinence. The true cause of the low graded inflammation remains unknown but the lack of triggering agents and the presence of T-cells and IL–8 might indicate some sort of local immunity or a local sensitization of nociceptors with hyperalgesia. IL-8 may in this respect act as a nociceptor sensitizer known from other inflammatory reactions.
It is obvious that urgency and urgency incontinence is a physiological phenomenon and the psychological augmentation often discussed in this context may also be the result of a true physiological stimulus.
The focus on the detrusor muscle as a trigger of urgency incontinence may not be correct and the use of muscarine antagonists should be re-evaluated.

Concluding message

It seems highly possible that low grade inflammatory changes in the urethra are the origin of urgency symptoms in the so called OAB-syndrome.
The true cause of this inflammatory response remains to be revealed.
Interleukin 8 seems to play a major role and may act as a sensitizer and/or trigger for nociceptors resulting in urgency.

Treatment of urgency incontinence should be focused on this inflammatory reaction and the afferent neurons from the urethra. The very concept of the OAB – syndrome and the rationales of treating “OAB-symptoms” with muscarine inhibitors might be questioned.

Specify source of funding or grant	**No diclosures, no grants**
Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**No**
This study did not require eithics committee approval because	**The study is summary of results obtained for clinic reasons after informed consent including written information and according to the rules of the Helsinki declaration. The ethical committee of the University has let known that an expanded study may be judged as a drug trial and an application has been prepared for such a study.**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**